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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/824,593	04/15/2004	Raymond Pratt	109536.159WO1	6645

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EXAMINER	
CHANNAVAJJALA, LAKSHMI SARADA	
ART UNIT	**PAPER NUMBER**
1615	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/824,593	PRATT ET AL.	
	Examiner	Art Unit	
	Lakshmi S. Channavajjala	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 9-28-07.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 25-45 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 25-45 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 9/28/07
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of amendment and remarks all dated 9-28-07 is acknowledged.

Claims 25-45 are pending in the instant application.

The following rejection of record has been maintained:

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 25-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/39000 (WO) in view of US 5,278,176 to Lin or WO in view of Buccafusco et al (Brain Research). Applicants have cited WO and Buccafusco on PTO-1449, however, a full article of Buccafusco have been attached to this action.

WO teaches methods of treating disorders of attention or improving attention by administering an effective amount of a cholinesterase inhibitor. WO teaches that acetylcholine is a neural transmitter for transmitting messages across the synapse to a cholinergic message by stimulating the cholinergic receptor for neuronal messages such as memory (page 3, L 23-29). WO teaches that cholinesterase rapidly destroys acetylcholine resulting in a weak cholinergic stimulation, experienced as a memory loss, and states that one way to overcome the above loss is to interfere with the ability of cholinesterase to degrade acetylcholine, as by treatment with a cholinesterase inhibitors (page 4, l 5-12). WO teaches all of the instant claimed compounds, including donepezil, for their cholinesterase inhibiting activity and thus inhibiting memory loss (pages 5+).

WO fails to teach the claimed method of treating substance abuse or treating withdrawal symptoms or decreasing the rate of relapse.

Lin teaches selective and potent nicotinic agonists that are useful in treating dementias, attention disorders, and anxiety associated with cognitive impairment or substance abuse withdrawal characterized by decreased cholinergic function (abstract). Lin teaches that chronic alcoholism (reads on instant substance abuse, see instant claim 36) and the resultant brain disease such as Alzheimer's disease, is characterized by diffuse reductions in cortical cerebral blood flow in those brain regions where cholinergic neurons arise (col. 2, L 61-65). Lin further states that nicotine withdrawal syndrome associated with tobacco use is characterized by craving for nicotine, irritability, frustration, anger, difficulty in concentration etc (col. 4, L 60-67). Lin suggests that symptoms associated with withdrawal of nicotine or compounds that act as nicotine agonists for acetylcholine receptors can alleviate other addictive substances.

Buccafusco et al studied the prevention of precipitated withdrawal symptoms by activating cholinergic systems during a dependence-producing schedule of morphine in rats. Buccafusco teaches that central cholinergic neurons have long been suggested to mediate many of the signs and symptoms of opiate withdrawal, profoundly affected by morphine and related drugs (page 76, col. 2 through page 77, col.1). Buccafusco observed that the many of the withdrawal symptoms such as body shakes were significantly reduced by treatment with cholinergic drugs (page 81, section 3.41). Buccafusco also observed that the AchE (acetylcholine esterase) activity was reduced

upon administration of DFP (diisopropylfluorophosphate), a cholinesterase inhibitor. Buccafusco further observed a significant reduction in each of the spontaneous morphine induced withdrawal symptoms, post-withdrawal blood pressure and the accompanying loss in body weight (page 81).

Thus, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to use the cholinesterase inhibitors such as donepezil and other compounds of treating substance abuse or withdrawal symptoms associated with substance abuse because both Lin and Buccafusco emphasize that the cholinergic system plays a profound role in substance abuse or drug withdrawal symptoms that are associated with substances such as alcohol or morphine (both of which are claimed to cause substance abuse) and that cholinesterase inhibitors effectively interfere with and alleviate the substance abuse and the associated withdrawal symptoms. Thus, on of an ordinary skill in the art would have expected the cholinesterase inhibitors of WO to be effective in reducing the substance abuse or in interfering with the drug withdrawal symptoms caused by abusive drugs such as nicotine, morphine, alcohol etc.

While Lin or Buccafusco does not teach al of the claimed drugs that result in the abuse or cause the withdrawal symptoms, both of them teach the underlying mechanism that results in the claimed abuse and its withdrawal symptoms and hence a skilled artisan would have expected to effectively reduce substance abuse, caused by any substance, with the cholinesterase inhibitors of WO. Further, optimizing the amount and the route of administration of the compounds of WO, so as to reduce substance

addiction and also prevent the return to drug seeking behavior would have been within the scope of a skilled artisan.

Response to Arguments

Applicant's arguments filed 9-28-07 have been fully considered but they are not persuasive.

Applicants' arguments are as follows:

WO 98/39000 (WO) describes the compounds of the claimed invention, i.e., donepezil and compounds of Formula (I) but does not disclose or suggest (i) a method for treating substance abuse in a patient in need thereof comprising administering a therapeutically effective amount of donepezil or a pharmaceutically acceptable salt thereof. **Lin** does not cure the deficiencies of WO 98/39000 because Lin is directed to compounds that are nicotinic agonists (see Lin at Abstract; column 1, lines 5-8; column 6, lines 58-60; column 21, lines 58 to column 22, line 25; column 22, lines 55-62). The invention claimed in the instant application is directed to the use of compounds that are cholinesterase antagonists (i.e., cholinesterase inhibitors). Moreover, Lin's compounds are structurally unrelated to the claimed compounds (i.e., donepezil, compounds of Formula (I)). There is no teaching or suggestion in Lin which would lead one of skill in the art to conclude that the nicotine derivative agonists described therein may be substituted with the cholinesterase antagonists of the instant claims. Therefore, Lin in combination with WO 98/39000 does not render the claimed invention obvious. Buccafusco does not cure the deficiencies of WO 98/39000.

Applicants' arguments are not persuasive because Lin has not been cited for the compounds that are claimed. Lin teaches that a number of diseases are characterized by the decreased cholinergic function, including cognitive impairment, substance abuse, withdrawal symptoms caused by the cessation of long term use of tobacco products and other addictive substances (technical field). Lin states that cognitive impairment due to organic brain disease is directly related to alcoholism and that of all the neurotransmitter systems studied, the neurotoxic effects of alcohol on the cholinergic system are thought to be the most important (lines bridging col. 2-3). Lin suggests improving the cognitive abilities, anxiety, dementia and withdrawal symptoms by improving the cholinergic function. Thus, Lin suggests the biochemical mechanism involved in improving the cholinergic function, which is directly related to the amelioration of the withdrawal symptoms to addictive substances such as alcohol, tobacco and other drugs. Even though the compounds used by Lin to improve the cholinergic function are not the same as claimed or related to the claimed compounds, both WO and Lin recognize the importance of cholinergic pathway in neuronal function (pages 3-4 of WO). WO further states that the claimed compounds possesses cholinesterase inhibiting activity, with very high specificity to acetyl cholinesterase, the predominant form of the enzyme in the brain. Applicants' invention is also based on the same cholinesterase inhibiting activity of the compounds. Accordingly, the combination of the above prior art does teach the instant claimed methods.

Applicants argue that Buccafusco teaches that administering diisopropylfluorophosphate or echothiophate to rats during the induction of morphine dependency resulted in reduction of certain symptoms associated with naloxone precipitated withdrawal. It is argued that Diisopropylfluorophosphate and echothiophate are organophosphate compounds and that the claimed compounds (i.e., donepezil and the compound of Formula (I)) are not organophosphate compounds and have chemical structures that are unrelated to Buccafusco's compounds. It is argued that there is no structural relationship between Buccafusco's compounds and the claimed compounds that would motivate one skilled in the art to select the compounds of the instant claims. It is argued that the Examiner's reliance on the mechanism of action is insufficient to support a prima facie obviousness rejection and that in an unpredictable field like chemistry; one skilled in the art would not expect compounds with completely different structures to have the same activity and mechanisms of action for treating any particular disease or disorder. Applicants' arguments are not persuasive because while it is true that structurally dissimilar compounds may not be expected to have similar properties, in the instant case, one of an ordinary skill in the art would have expected the compounds of WO to be effective for the claimed method of treatment because there is a nexus between the mechanism of action of the compounds and the claimed conditions caused due the same mechanism. The prior art cited clearly establishes the role of cholinergic system in substance abuse and interfering with the cholinergic system, in order to improve the conditions associated with substance abuse. The prior

also recognizes the claimed compounds are capable of interfering with the cholinergic system.

With respect to the argument that the compounds described in Buccafusco do not achieve the same anti- withdrawal effect that the Examiner is relying on for the obviousness rejection, Buccafusco states in the introduction section that cholinergic neuron play a role in the signs and symptoms of opiate withdrawal and that morphine and the related drugs have a profound inhibitory action on peripheral and central cholinergic neurons, and that during withdrawal the enhanced function of brain and spinal cholinergic neurons appears to contribute significantly to the expression of behavioral and autonomic withdrawal symptoms. Further, Buccafusco states that on page 81 that the withdrawal symptoms such as body shakes and the expression of cholinergic receptors were significantly reduced with DFP treatment. Buccafusco also states that not all of the withdrawal symptoms are linearly expressed with the magnitude of withdrawal and therefore the argument that the anti-withdrawal effects are compound specific is not persuasive. One can clearly recognize from the teachings of Buccafusco that not all of the withdrawal symptoms are equally expressed and hence such symptoms constitute a limitation in determining the effect on reducing the withdrawal symptoms. Buccafusco further recognizes that the effectiveness of a compound in suppressing the withdrawal symptoms is also a function of the receptor selectivity relative to the AchE inhibitors. Thus, a skilled artisan would have expected variations in the effectiveness of different acetyl cholinesterase inhibitors in reducing the withdrawal symptoms to a given substance or drug and yet the utility the cholinesterase inhibitors in

interfering with the withdrawal symptoms in substance abuse in unquestionable as recognized by Buccafusco.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S. Channavajjala whose telephone number is 571-272-0591. The examiner can normally be reached on 7.00 AM -4.00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AU 1615

December 13, 2007

LAKSHMI S. CHANNAVAJJALA
PRIMARY EXAMINER